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Randomized Trial of Trimethoprim-Sulfamethoxazole versus Pyrimethamine-Sulfadiazine for Therapy of Toxoplasmic Encephalitis in Patients with AIDS

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The aim of the present pilot study was to compare the efficacy and safety of trimethoprim (TMP) and sulfamethoxazole (SMX) with those of the standard therapy pyrimethamine (P)-sulfadiazine (S) for the treatment of toxoplasmic encephalitis in patients with AIDS. This was a pilot, multicenter, randomized, and prospective study. Patients were randomly assigned to receive TMP (10 mg/kg of body weight/day) and SMX (50 mg/kg/day) or P (50 mg daily) and S (60 mg/kg/day) as acute therapy (for 4 weeks) and then as maintenance therapy for 3 months at half of the original dosage. Seventy-seven patients were enrolled and randomized to the study: 40 patients were treated with TMP-SMX and 37 were treated with P-S. There was no statistically significant difference in clinical efficacy during acute therapy. In contrast, patients randomized to TMP-SMX appeared more likely to achieve a complete radiologic response after acute therapy. Adverse reactions were significantly more frequent in patients treated with P-S, and skin rash was the most common adverse event noted in these patients. In conclusion, the results of the study suggest that TMP-SMX appears to be a valuable alternative to P-S, in particular in patients with opportunistic bacterial infections.

Encephalitis caused by *Toxoplasma gondii* (toxoplasmic encephalitis [TE]) is the most common opportunistic infection causing focal brain disease in patients with AIDS (15, 16). More than 95% of cases of TE are strictly related to reactivation of a chronic (latent) infection, usually when the CD4-positive T-lymphocyte count falls below 100 cells/mm^3 (17). The incidence of TE depends on the prevalence of *T. gondii* infection in the general population; in the United States 5 to 10% of the AIDS patients who are anti-*T. gondii* immunoglobulin G positive will develop TE (17), whereas in Europe, it is estimated that TE will develop in 10 to 40% of AIDS patients (20). The current recommended therapy for TE is the synergistic combination of pyrimethamine (P) and sulfadiazine (S) (14, 17). Unfortunately, successful treatment of patients with a severely impaired immune system, such as AIDS patients, with P-S is associated with adverse reactions, particularly to the sulfonamide component, that may preclude their use in up to 40 to 50% of patients (6, 12). New antitoxoplasma drugs are needed because of the frequency of adverse reactions with the current drugs and the low level of activity of the current drugs against the cyst form of *T. gondii* and because drugs with improved pharmacokinetic properties, including greater bioavailability and higher and more persistent levels in serum and/or in the cell, are needed. Several studies have shown that trimethoprim (TMP)-sulfamethoxazole (SMX) is effective for the primary prophylaxis of TE in patients with CD4 cell counts of less than 100 cells/mm^3 and positive serology (2, 18). In addition, the Centers for Disease Control and Prevention (3) recommended TMP-SMX for the primary prophylaxis of TE in AIDS patients with CD4 cell counts of less than 100 cells/mm^3. However, the efficacy of TMP-SMX in the therapy of AIDS patients with TE has not yet been established. On the other hand, TMP-SMX has been shown to be effective against *T. gondii* in a variety of animal models (8, 10, 11), and several small nonrandomized studies have shown the beneficial effect of TMP-SMX in AIDS patients with TE (1, 13, 22). These promising in vitro and in vivo results from the use of TMP-SMX for the treatment of TE prompted us to undertake a prospective, multicenter, randomized, pilot trial to evaluate the effectiveness and safety of TMP-SMX as an alternative therapy for TE in patients with AIDS.

MATERIALS AND METHODS

Study design. A prospective, multicenter, randomized, pilot study was designed to compare standard therapy for TE (P-S) to TMP-SMX therapy. The protocol was approved by the investigational ethics committee at each center before the study started, and informed consent was obtained from each patient.

Recruitment and eligibility of patients. AIDS patients, infected with human immunodeficiency virus type 1 with signs, symptoms, and computed tomography or magnetic resonance imaging scans judged compatible with the diagnosis of TE, were randomized to receive either P-S or TMP-SMX. Patients were eligible to enter the study if they were >18 years of age, had no known or suspected allergy to the study drugs, were not pregnant, and did not have *Pneumocystis carinii* pneumonia or a concomitant infection of the central nervous system. Patients were excluded from the study for a previous episode of TE, previous treatment or prophylaxis with TMP-SMX, or a poor hematological profile defined as a neutrophil count of $<0.75 \times 10^9$/liter, a hemoglobin level of <8 g/dliter, and/or a platelet count of $<50 \times 10^9$/liter.

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TABLE 1. Demographic and clinical baseline characteristics of patients with TE

Characteristics	P-S (n = 37)	TMP-SMX (n = 40)	P value
Mean age (yr)	32.4 ± 4.5	34.0 ± 6.4	0.21
Male (no. [%] of patients)	29 (78.4)	28 (70.0)	0.44
Female (no. [%] of patients)	8 (21.6)	12 (30.0)	0.44
Risk factors for AIDS (no. [%] of patients)			
Intravenous drug abuse	30 (81.0)	30 (77.0)	0.58
Homosexual contacts	3 (10.1)	3 (7.7)	1.0
Heterosexual contacts	4 (11.0)	6 (15.2)	0.73
Blood transfusion	0	1 (2.5)	<0.0001
No. (%) of patient with the following:			
Fever	21 (58.3)	21 (51.2)	0.81
Headache	26 (72.2)	21 (51.2)	0.16
Seizures	8 (22.2)	14 (34.1)	0.21
Lethargy-coma	1 (2.7)	5 (12.1)	0.20
Hemiplegia or hemiparesis	17 (47.2)	22 (53.6)	0.49
Brain imaging findings (no. [%] of patients)			
Single lesion	11 (30.6)	18 (43.9)	0.23
Multiple lesions	25 (69.4)	23 (56.1)	0.48

Treatment arms. By means of a computer-generated sequence, each patient was randomly assigned to receive either of the two regimens. The first regimen consisted of P-S given orally or via a nasogastric tube (in comatose patients) for 30 days. The dosage of P was 50 mg daily, and that of S was 60 mg/kg of body weight/day. In addition, folinic acid was given in a single dosage of 10 mg/day for the whole course of therapy. The second regimen consisted of TMP-SMX given orally or given intravenously if the patient was comatose, critically ill, or unable to take the drugs by oral administration. The dosages were the same for both routes of administration: 10 mg of TMP per kg/day plus 50 mg of SMX per kg/day every 12 h for 30 days.

After a 30-day course of acute therapy, the patients were continued on maintenance therapy at a reduced dosage (50%) for a further 3 months. Supportive treatment included use of steroids in those patients treated with TMP-SMX or P-S who showed at computed tomography evidence of perilesional edema and/or lesions that cause a mass effect. In addition, during the study patients treated with TMP-SMX or P-S did not receive any antiretroviral therapy. Patients were classified as having completed therapy if they received 80% of the total dose of P-S or TMP-SMX. Patients were crossed over to the other arm of treatment if they either had not responded within 15 days or had serious adverse reactions.

Monitoring, diagnosis, and evaluation of response. During acute therapy patients underwent complete clinical and neurologic examinations and laboratory evaluation at the time of study entry and at weeks 1, 2, 3, and 4. Laboratory evaluation including blood cell count, serum chemistry analysis, and liver and renal tests were performed at the same times at the clinical evaluation. Computed tomography or magnetic resonance imaging were performed blindly by the radiologist at the time of study entry and at the end of acute therapy (after 30 days). Adverse reactions were scored by means of the World Health Organization scale for toxic effects. Mild-to-moderate adverse events (grades 1 and 2) were treated symptomatically. For patients with severe toxic effects (grades 3 and 4) the drug treatment was stopped. During the maintenance therapy patients underwent clinical, neurologic, and laboratory evaluations every month. A diagnosis of TE was based on signs and symptoms of central nervous system dysfunction and typical lesions on computed tomography or magnetic resonance imaging (24). Clinical efficacy was defined as follows: complete response, resolution of neurologic signs and symptoms related to TE; partial response, decrease of active signs or symptoms of TE; no change or progression, lack of any improvement or increasing severity of neurologic and clinical signs. The same criteria were used for the radiologic evaluation of efficacy, as follows: complete response, a normal result or complete resolution of all initial lesions and absence of any new lesions; partial response, more than 50% decrease in the number of lesions and the absence of any new lesions; no change or progression, no decrease in the number and/or size of the brain lesions or an increase in the number of lesions and/or the size of any initial lesions. Neuroradiographic scans were performed at 4 weeks or sooner if the patient discontinued therapy because of clinical progression of disease or toxicity.

Statistical analysis. Data are expressed as means and standard deviations. The overall incidence and severity of adverse reactions and therapeutic outcome were compared by Fisher's exact test. P values of <0.05 were considered statistically significant.

TABLE 2. Clinical response at the end of acute therapy for TE[a]

Treatment response	No. (%) of patients	
	P-S (n = 35)	TMP-SMX (n = 37)
Complete	23 (65.7)	23 (62.1)
Partial	7 (20.0)	8 (21.6)
No change or progression	5 (14.2)	6 (16.2)

[a] Data are not statistically significant.

RESULTS

Seventy-seven patients were enrolled and randomized for examination of the efficacy and tolerability of the study medications (37 patients were assigned to the P-S arm and 40 were assigned to the TMP-SMX arm). Table 1 presents the demographic and clinical characteristics of patients with TE at the time of study entry. Most of the patients were men (75%), and the mean age was 33.2 ± 5.6 years. The CD4 T-cell count was not available at the time of entry into the study. Thirty-one of 40 (75.6%) patients treated with TMP-SMX had antibodies (immunoglobulin G) to *T. gondii*, whereas 29 of 37 (80.5%) patients treated with P-S had a positive serology. Six patients were comatose at the time of entry into the study. One patient was treated with P-S via a nasogastric tube, whereas five patients were treated with TMP-SMX by the intravenous route. In addition, seven patients were also treated intravenously with TMP-SMX, inasmuch as their clinical conditions did not allow oral administration of the drug. Thirty-five of 40 patients in the group treated with TMP-SMX and 33 patients of 37 patients in the group treated with P-S were also treated with dexamethasone, inasmuch as they showed at computed tomography brain lesions surrounded by edema. However, the clinical and radiologic improvements in patients given P-S or TMP-SMX intravenously were similar. The clinical response to therapy with P-S or TMP-SMX was evaluated at the end of the acute therapy (after 30 days). Three patients treated with TMP-SMX and four patients treated with P-S crossed over to the other treatment arm of the study because they did not respond to treatment. All patients treated with TMP-SMX or with P-S who crossed over showed a complete or partial response according to clinical and radiologic signs at the end of the acute therapy. As shown in Table 2, a complete clinical response was observed in 23 (65.7%) patients treated with P-S and in 23 (62.1%) patients treated with TMP-SMX; there was a lack of response or progression of the disease in 5 (14.2%) patients in the P-S group and in 6 (16.2%) patients in the TMP-SMX group. Seventy of 77 patients had a radiologic evaluation at the end of acute therapy (Table 3). A complete resolution of radiologic lesions was noted in 13 (39.3%) patients randomized to P-S

TABLE 3. Radiologic response at the end of acute therapy for TE

Treatment response	No. (%) of patients	
	P-S (n = 33)	TMP-SMX (n = 37)
Complete	13 (39.3)	23 (62.1)
Partial	10 (30.3)	4 (10.8)
No change or progression	10 (30.3)	10 (27.0)

[a] P = 0.0478.

TABLE 4. Adverse reactions in AIDS patients with TE during the acute and the maintenance therapy

Adverse reaction	No. (%) of patients		
	TMP-SMX (n = 40)	P-S (n = 37)	P value
Any of at least one adverse reaction	5 (12.5)	8 (21.6)	0.36
Fever	0	1	0.48
Skin rash	0	6	0.0098
Diarrhea	1	0	1.00
Gastric disturbances	0	2	0.22
Vomiting	0	1	0.48
Toxic effect on liver	1	1	1.00
Toxic effect on kidneys	0	1	0.48
Leukopenia	1	0	1.00
Neutropenia	1	1	1.00
Thrombocytopenia	0	1	0.48
Pancytopenia	1	0	1.00
Total	5 (12.5)	14 (37.8)	0.00162

and in 23 (62.1%) patients randomized to TMP-SMX (P = 0.0478). In addition, a partial resolution of radiologic lesions was observed in 10 (30.3%) patients randomized to P-S and in 4 (10.8%) patients randomized to TMP-SMX. A lack of resolution of brain lesions or progression was observed in 10 (30.3%) patients randomized to P-S and in 10 (27%) patients randomized to TMP-SMX. It should be noted that we lost 5 patients and 7 patients for clinical and radiologic evaluations, respectively, at day 30.

The rate of relapse (worsening of clinical and/or radiologic signs) was evaluated during the maintenance therapy period. During the 3-month period, one relapse was observed in the 37 patients treated with TMP-SMX, but no relapses were observed in the 35 patients treated with P-S. Survival did not significantly differ between the two groups. No patient in either treatment arm died during the acute therapy period. Two patients died during the maintenance therapy; one patient randomized to the P-S group died of sepsis due to *Staphylococcus aureus* after 2 months of maintenance therapy, and one patient randomized to the TMP-SMX group died of decompensated posthepatic cirrhosis after 3 months of maintenance therapy. Adverse reactions occurred more frequently in the group of patients treated with P-S (Table 4): 14 (37.8%) in the P-S group and 5 (12.5%) in TMP-SMX group (P = 0.0162). Skin rashes were observed only in the P-S group.

DISCUSSION

This randomized, pilot trial provides the first prospective data on the efficacy and toxicity of therapy with TMP-SMX for TE in AIDS patients. Our results have shown that TMP-SMX is effective for the treatment of TE. The presence of antibodies to *T. gondii* was not required as an inclusion criterion, given the high prevalence of positivity found in Europe and the fact that TE was not unequivocally associated with positive toxoplasma serology at the time that the study was designed. In our study we observed a substantially lower rate of response of radiologic lesions in comparison with that for clinical signs. The radiologic response to therapy lags behind the clinical response. In particular, especially during the first 2 to 3 weeks, a disparity between the radiologic and clinical responses may be observed, when there is clinical improvement, despite the progression found in neuroradiologic studies. Adverse reactions were significantly frequent in the group of patients treated with P-S. Several studies have shown that in AIDS patients, treatment of TE must consist of both primary and maintenance therapy because of the 30 to 50% rate of relapse (12, 19, 24). It has been demonstrated that there is a wide range of doses of P-S which are effective for acute therapy of TE: 25 to 100 mg of P and 2 to 8 g of S (5–7). In addition, three small nonrandomized studies evaluated the efficacy of TMP-SMX in AIDS patients with TE (1, 13, 22). The dosage of TMP varied from 6.6 to 20 mg/kg/day, with the rate of efficacy ranging from 41.6 to 100%. In one of the three studies, Canessa et al. (1) showed clinical and radiologic responses in 9 of 12 patients (75%) treated with two different dosages of TMP-SMX (6.6 or 20 mg/kg/day). Recently, Winstanley et al. (25) have observed marked variations in the bioavailability of P in AIDS patients treated for TE, and the investigators suggest that a parenteral formulation of P would overcome variations in bioavailability. On the other hand, Chin et al. (4) have demonstrated that TMP-SMX, when given orally, is well absorbed in critically ill patients with AIDS, and no significant difference in the area under curve was observed between the intravenous and oral doses. Sattler et al. (21) reported that for AIDS patients a mean daily intravenous dose of 12 $\pm$ 3.4 mg of TMP per kg produced levels in serum of between 5 and 8 μg/ml, which resulted in decreased toxicity, without a decrease in efficacy. In addition, several studies have shown that TMP-SMX has good penetration in cerebrospinal fluid in individuals with either infected or healthy meninges (9, 23). In our study the adverse reaction rate observed in patients treated with TMP-SMX was significantly lower than that observed in patients treated with P-S. In particular, skin rash was not observed in any patients treated with TMP-SMX. The absence of rash among TMP-SMX-treated patients could be related to the low dosage used to treat our patients. Therefore, the use of TMP-SMX could represent a good therapeutic alternative for TE therapy in AIDS patients. Moreover, although this study was not designed for this aim, maintenance therapy with TMP-SMX in AIDS patients with TE may also prevent opportunistic infections susceptible to these drugs (16), including pneumonia due to *P. carinii*, and bacterial infections caused by *Salmonella* spp., *Listeria monocytogenes*, *Legionella* spp., and some unusual infections caused by *Nocardia* spp., *Pseudomonas cepacia*, and *Pseudomonas maltophilia* (26). In conclusion, this study showed that TMP-SMX is a reliable alternative to P-S therapy, and it may represent an effective drug for the therapy of bacterial opportunistic infections.

APPENDIX

Members of the Italian Collaborative Study Group are as follows. Coordinators: G. P. Fiori (Varese), G. Carosi (Brescia). Members: D. Torre and F. Speranza (Division of Infectious Diseases, Varese); S. Casari, G. Gregis, and A. Donisi (Institute of Infectious Diseases, Brescia); A. Orani and M. Nigro (Division of Infectious Diseases, Lecco); F. Suter and F. Maggiolo (Division of Infectious Diseases, Busto Arsizio); G. P. Cadeo and B. Morandini (Division of Infectious Diseases, Mantova); A. Poggio (Division of Infectious Diseases, Verbania-Pallanza); G. Scalise and F. Ancarani (Institute of Infectious Diseases, Ancona); G. Angarano and P. Maggi (Institute of Infectious Diseases, Bari); G. Chiodo and G. Marinacci (Institute of Infectious Diseases, S. Orsola Hospital, Bologna); F. Gritti and M. G. Catalini (Division of Infectious Diseases, Maggiore Hospital, Bologna); A. Scalzini and R. Stellini (Division of Infectious Diseases, Brescia); F. Ghinelli (Division of Infectious Diseases, Ferrara); S. Pauluzzi and F. Menichetti (Institute of Infectious Diseases, Perugia); F. Al-

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